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REMARKS

Claims 16-28 are under consideration. An Appendix of the pending claims is attached for the Examiner's convenience. The following comments are put forth at this time in response to the final rejection of the claims. Favorable consideration of the following comments relative to the outstanding rejections as they may apply to the present claims is respectfully requested for the reasons that follow.

Claims 16-22 and 28 stand rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 5,639,595 to Mirabelli *et al.* (MIRABELLI) in view of Kaufman, Meth. Enzymol. 185:487-511 (KAUFMAN). Applicants respectfully traverse the rejection.

MIRABELLI is generally directed to the generation of random oligonucleotides as antisense molecules, and in particular, as antisense molecules to infectious agents, such as bacteria.

The rejection is based on the proposition that MIRABELLI at Column 15, lines 40-45 discloses a library of random oligonucleotides expressed from plasmid vectors that integrate into a mammalian host cell genome and direct the synthesis of MRP protein, which is expressed at the cell-surface. Applicants respectfully disagree and assert that MIRABELLI discloses that MRP is expressed from a cellular gene and that MRP expression is inhibited by random oligonucleotides expressed from plasmid vectors.

Column 15, lines 38-55 states:

> Selection of cells containing active oligonucleotides which inhibit cell surface expression of MRP.
>
> Selection of individual cells containing active oligonucleotide occurs when the cell population is treated with antibodies directed towards MRP and subsequently treated with complement. Hood, L.E., Weissman, I.L., and W.B. Wood. *Immunology* pp. 161-164; Benjamin/Cummings Publishing Co., Inc., 1978. The cell surface expression of MRP causes antibody-complement-mediated lysis of cells expressing MRP. Cells in which MRP expression has been inhibited by oligonucleotide are not affected. This allows the recovery of those cells in which expression of the MRP protein has been inhibited by oligonucleotide. These cells are then recovered and allowed to recover and expand in culture. The oligonucleotides contained within them are identified by plasmid isolation or PCR amplification and DNA sequence of clonal populations of individual recovered cells using the Sanger dideoxy sequencing method.

Two phrases within the above passage indicate that MRP expression is inhibited by the random oligonucleotides of MIRABELLI. Column 15, lines 38-39 and lines 47-48 state, respectively: "Selection of cells containing active oligonucleotides which inhibit cell surface expression of MRP", and "Cells in which MRP expression has been inhibited by oligonucleotide".

Furthermore, Example 2, from which the above-passage is quoted, is entitled: "Identification of random oligonucleotides which inhibit expression of the multidrug resistance-associated protein (MRP)" (*see* Column 14, lines 64-65). Thus, MRP is inhibited rather than expressed by the random oligonucleotide library.

Further support of Applicants' position is found at Column 15, lines 3-10:

> One cause of multidrug resistance is believed to be overexpression of a member of the ATP-binding cassette transmembrane transporter superfamily known as multidrug resistance-associated protein (MRP). This protein is overexpressed in certain tumor cell lines, such as H69AR, which are multidrug resistant. Cole et al. (1992) Science 258:1650-1654; Slovak et al., (1993) Cancer Res. 53:3221-3225. MRP is expressed on the cell surface.

The origin of the multidrug resistant cell line, H69AR, used in the procedure described at Column 15, lines 38-55 is provided at Column 15, lines 27-29: "H69AR, a doxorubicin-resistant human small cell lung carcinoma cell line, is selected and maintained as described by Mirski *et al.* (1987) Cancer Res. 47:2594-2598." (MIRSKI). Enclosed herein as Exhibit A is the abstract of MIRSKI which describes the selection and isolation of H69AR:

> A multidrug resistant variant (H69AR) of the human small cell lung cancer cell line NCI-H69 was obtained by culturing these cells in gradually increasing doses of Adriamycin up to 0.8 microM after a total of 14 months. H69AR expressed the multidrug resistant phenotype because it is cross resistant to anthracycline analogues including daunomycin, epirubicin, menogaril, and mitoxantrone as well as to acivicin, etoposide, gramicidin D, colchicine, and the Vinca alkaloids, vincristine and vinblastine.

In view of Exhibit A, Applicants respectfully assert that MRP is expressed by an H69AR cellular gene rather than being encoded and expressed by the plasmid library of MIRABELLI. To further support this assertion, MIRABELLI states at Column 15, line 31: "Cells are transfected with the expression library using standard calcium phosphate methods." The "Cells" referred to in this passage are H69AR cells (*see* Column 15, lines 27-30) and the "expression library" is the plasmid library of random antisense oligonucleotides (*see* Column 15, lines 11-24). Therefore, H69AR cells expressed MRP prior to their transfection with the plasmids of MIRABELLI.

Applicants respectfully submit that the Examiner, in asserting that MRP is encoded by the transfected expression library, may have misinterpreted the sentence at Column 15, lines 31-32: "Positively transfected cells [H69AR] are selected by drug resistance." Applicants respectfully point out that this sentence does not relate to the drug resistance associated with MRP but relates to a drug resistance marker encoded by the plasmid vector which facilitates the selection and isolation of cells transfected with the library that expresses random

oligonucleotides. An example of a plasmid-based drug-selection system is described at Column 14, lines 54-55: "Stable transformants will be selected on the basis of resistance to G418." Thus, the drug resistance imparted on the H69AR cells by plasmid library transfection does not relate to MRP but does provide a convenient selectable marker for enrichment of transfected cells.

In further support of Applicants' position that the plasmid library of MIRABELLI does not express peptides, the Examiner is respectfully directed to Column 15, lines 11-18 which describes the cassette used for the expression of a random oligonucleotide library:

> Synthesis of a random library.
> The expression cassette, . . . (SEQ ID NO:1), was synthesized by standard phosphoramidite chemistry on an automated DNA synthesizer. The expression cassette encodes restriction sites at the 5' and 3' ends of the oligonucleotide, the T7 RNA polymerase promoter, an RNAse P1 recognition structure and a 14-base random sequence.

Therefore, the expression cassette of MIRABELLI contains an RNA polymerase promoter for the transcription of the plasmid DNA into RNA but it does not contain sequences to permit the translation of the RNA transcript into protein. Absent from the plasmids of MIRABELLI is a teaching or suggestion of sequences such as an initiator methionine codon, a Kozak's consensus sequence, or other types of sequences which are known in the art to enable translation of an RNA transcript into a peptide. Thus, MIRABELLI teaches away from peptide expression and is limited to oligonucleotide expression.

Lastly, in response to the Examiner's assertion that the plasmid library of MIRABELLI is incorporated into a host cell genome, Applicants respectfully point out that MIRABELLI does not describe sequences or methods to facilitate the incorporation of the plasmid library into the genome of a host cell; nor does MIRABELLI teach or suggest that incorporation of the plasmid library is desirable for practicing random oligonucleotide expression. Rather, MIRABELLI teach that the plasmid may be isolated from cells that had been transfected with the library (Column 15, lines 50-53). By stating that the plasmid is isolated from a transfected cell, MIRABELLI indicates that the transfected plasmid is maintained in an episomal state and is not incorporated into the genome following its introduction into a host cell.

However, the Examiner's position appears to be that the plasmid library of MIRABELLI is incorporated into the genome of H69AR cells because expression of the transfected plasmid library requires that it be incorporated into the H69AR genome. Applicants respectfully assert that this is incorrect and maintain that expression from the transfected plasmids of MIRABELLI

does not require that they be incorporated into the H69AR genome. As outlined above and at Column 15, lines 11-24, the plasmids of MIRABELLI contain a T7 RNA polymerase promoter for the transcription of the downstream, random plasmid sequences to produce a random library of oligoribonucleotides (*see* Column 15, lines 33-37). The plasmid library of MIRABELLI contains the requisite sequences for transcription whereby the random oligonucleotide library is produced. Thus, transcription of plasmid sequences does not require plasmid integration.

Based on the foregoing, Applicants contend that MIRABELLI describes a random library of oligonucleotides expressed from a plasmid vector; cells transfected with the plasmid library; and methods of use. MIRABELLI does not teach or suggest a molecular library of nucleic acids encoding a plurality of randomized peptides; a molecular library of retroviruses; a cellular library of mammalian cells containing a molecular library of retroviral constructs; or a cellular library of mammalian cells in which the retroviral constructs are integrated into a cellular genome.

Turning now to KAUFMAN, Applicants respectfully assert that KAUFMANN does not add substantially to MIRABELLI. KAUFMAN does describe retrovirus vectors and enumerates a number of their advantages that relate to: i) the introduction of the nucleic acid contained within the retrovirus particle into a host cell; ii) the integration of the retroviral genome into the cellular chromosome; and iii) the various cell types that are susceptible to retrovirus infection. However, in contrast to these advantages, KAUFMAN does cite technical limitations (*see* page 495, lines 4-6) associated with retrovirus vectors that relate to polypeptide expression, propagation, and packaging.

Moreover, when viewed in the context of the claim elements, KAUFMAN does not teach or suggest a molecular library of retroviruses; a molecular library of retroviruses encoding a plurality of randomized peptides; a cellular library of mammalian cells containing a molecular library of retroviral constructs encoding a plurality of randomized peptides; or a mammalian cell library of retroviral constructs that have been incorporated into the genome of a cell.

As the Examiner is aware, the requirements for establishing a *prima facie* case of obviousness are: i) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; ii) there must be a reasonable expectation of success; and iii) the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991) M.P.E.P. §2143.

In the present case, the cited art, either alone or in combination, does not disclose each of the claimed elements. Neither MIRABELLI nor KAUFMAN disclose a library of randomized nucleic acids encoding a plurality of randomized peptides; a library of retrovirus vectors; a cellular library of mammalian cells containing a library of retrovirus vectors; or a cellular library of mammalian cells containing retrovirus vectors that have been incorporated into their genome. Therefore, the requirement of teaching or suggesting all the claim elements has not been met.

Moving to the issue of whether the disclosures suggest that the elements be combined, Applicants respectfully submit that the elements are not disclosed, therefore, there can be no suggestion that they be combined to arrive at the present invention.

Lastly, there is no reasonable expectation of success at arriving at the present invention by combining MIRABELLI and KAUFMAN. Neither MIRABELLI nor KAUFMAN teach or suggest the expression of a library of random peptides from a retrovirus library or methods of constructing a retrovirus library. Therefore, the skilled artisan would not be led to arrive at the present invention without undue experimentation from the disclosures of MIRABELLI and KAUFMAN.

In view of these remarks, Applicants respectfully submit that the references either alone or in combination do not support a conclusion of obviousness and respectfully request the rejection be withdrawn.

Claims 16-26 and 28 stand under 35 U.S.C. §103(a) as being unpatentable over MIRABELLI, in view of KAUFMAN and Nilsson *et al.* Curr. Opin. Struc. Biol. 2:569-575 (NILSSON). Applicants respectfully traverse the rejection.

Applicants respectfully submit that the arguments put forth above in response to the Section § 103(a) rejection of Claims 16-22 and 28 apply in traversing the rejection of Claims 16-26 and 28. NILSSON does not cure any of the defects with regards to MIRABELLI and KAUFMAN *vis-a-vis* a molecular library of nucleic acids encoding a plurality of randomized peptides; a molecular library of retroviruses; or a cellular library of mammalian cells comprising a library of retroviral constructs.

Therefore, Applicants respectfully submit that the references, either alone or combination, do not support a conclusion of obviousness and respectfully request the rejection be withdrawn.

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CONCLUSION

Applicants respectfully submit that the claims are now in condition for allowance and early notification to that effect is respectfully requested. If the Examiner feels there are further unresolved issues, the Examiner is respectfully requested to phone the undersigned at (415) 781-1989.

Respectfully submitted,

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APPENDIX:

16. (Amended) A molecular library of retroviruses comprising at least 10^4 different randomized nucleic acids encoding a plurality of randomized peptides.

17. (Amended) A molecular library of retroviruses according to claim 16 comprising at least 10^5 different randomized nucleic acids encoding a plurality of randomized peptides.

18. (Amended) A molecular library of retroviruses according to claim 16 comprising at least 10^6 different randomized nucleic acids encoding a plurality of randomized peptides.

19. (Amended) A molecular library of retroviruses according to claim 16 comprising at least 10^7 different randomized nucleic acids encoding a plurality of randomized peptides.

20. (Amended) A molecular library of retroviruses according to claim 16 comprising at least 10^8 different randomized nucleic acids encoding a plurality of randomized peptides.

21. (Amended) A cellular library of mammalian cells containing a molecular library of retroviral constructs, said molecular library comprising at least 10^4 different randomized nucleic acids encoding a plurality of randomized peptides.

22. A cellular library according to claim 21 wherein said constructs are integrated into the cellular genome.

23. A molecular library of retroviruses according to claim 16, wherein said nucleic acids further encode a fusion partner.

24. A molecular library of retroviruses according to claim 23, wherein said fusion partner comprises a targeting sequence.

25. A molecular library of retroviruses according to claim 23, wherein said fusion partner comprises a rescue sequence.

26. A molecular library of retroviruses according to claim 23, wherein said fusion partner comprises a stability sequence.

27. A molecular library of retroviruses according to claim 23, wherein said fusion partner comprises a dimerization sequence.

28. A molecular library of retroviruses according to claim 16, wherein said randomized n nucleic acids are biased in their randomization.